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Regional differences in adipose tissue metabolism in obese men

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Abstract

We examined omental and subcutaneous adipose tissue adipocyte size, and lipolysis and lipoprotein lipase (LPL) activity in a sample of 33 men aged 22.6 to 61.2 years and with a body mass index ranging from 24.6 to 79.1 kg/m^2. We tested the hypothesis that lipolysis rates would be higher in the omental fat depot than in subcutaneous adipose tissue and that this difference would persist across the spectrum of abdominal adiposity values. Omental and subcutaneous adipose tissue samples were obtained during surgery. Adipocytes were isolated by collagenase digestion. Adipocyte size and LPL activity as well as basal, isoproterenol-, forskolin-, and dibutyryl cyclic adenosine monophosphate–stimulated lipolysis were measured. Although adipocytes from both fat compartments were larger in obese subjects, no difference was observed in the size of omental vs subcutaneous fat cells. Lipoprotein lipase activity, expressed as a function of cell number, was significantly higher in omental than in subcutaneous fat tissue ($P < .005$). Basal lipolysis and lipolytic responses to isoproterenol, forskolin, or dibutyryl cyclic adenosine monophosphate, expressed either as a function of cell number or as a fold response over basal levels, were not significantly different in omental vs subcutaneous fat cells. When stratifying the sample in tertiles of waist circumference, adipocyte diameter was similar in the omental and subcutaneous depots for all adiposity values. Omental adipocyte size reached a plateau in the 2 upper tertiles of waist circumference, that is, from a waist circumference of 125 cm and above. Lipoprotein lipase activity was significantly higher in omental cells in the middle tertile of waist circumference ($P = .05$), and no regional difference was noted in lipolysis values across waist circumference tertiles. In conclusion, in normal-weight to morbidly obese men, although adipocyte size and lipolysis tended to increase with higher waist circumference, no difference was observed between the omental and subcutaneous fat depot.

1. Introduction

Visceral adipose tissue accumulation has been closely related to a cluster of metabolic alterations including insulin resistance, hyperinsulinemia, elevated triglyceride levels, low high-density lipoprotein (HDL) cholesterol and hypertension [1,2]. Intra-abdominal fat accumulation is, therefore, presumed to be a significant determinant of obesity-related metabolic complications, independently of total adiposity [2-4]. One of the predominant theories put forth to explain this association, the portal vein theory, is based on the particular characteristics and anatomic location of intra-abdominal fat depots and their venous drainage by the portal vein system [5]. Being highly responsive to catecholamine stimulation and poorly responsive to lipolysis inhibition by insulin, intra-abdominal adipocytes are usually thought to be hyperlipolytic [2,6-8]. Such visceral adipocytes are specifically prone to generate high free fatty acid flux in the portal vein, which would be critical in the emergence of obesity-related complications by enhancing triglyceride-rich lipoprotein synthesis in the liver, by stimulating hepatic gluconeogenesis, and by reducing insulin clearance [5,6].

Many studies have investigated the differences in lipolysis between intra-abdominal and subcutaneous adipocytes. Most of them, using either isolated adipocytes or tissue explants, showed higher basal lipolysis in subcutaneous fat tissue or cells [8-16]. Several studies also found that the maximal absolute response to the β-adrenergic agonist

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isoproterenol or epinephrine was higher in subcutaneous fat depots [8-11,13,16,17]. Few studies also showed the contrary [18]. As for incremental lipolytic stimulation above basal level by isoproterenol [12,14,16] or other cathecholamines [8,19], results generally indicated higher responses in omental vs subcutaneous fat tissue or cells. Among all these studies, different units were chosen to express lipolysis (per lipid weight, per cell number, per cell surface), which could have contributed to the inconsistencies among previous results on regional differences in lipolysis. In addition, obese and lean subjects or males and females were often combined in the analysis. Very few studies investigated whether regional differences in lipolysis were found in both obese and nonobese subjects. One of these studies reported that catecholamine-induced lipolysis (expressed in percent response) was higher in omental than in subcutaneous fat cells, but only in obese [19]. However, we recently reported that regional differences were relatively constant throughout the spectrum of adiposity values in a sample of women [16].

Lipoprotein lipase (LPL) activity has also been the topic of numerous studies [15-18,20-24]. Two studies reported higher LPL activity in omental fat [18,24] and 3 others indicated higher values in subcutaneous fat [15,16,23]. Three studies found no difference between the 2 depots [17,20,22]. Combining men and women or lean and obese subjects in the studies mentioned above could have contributed to the equivocal results obtained because of sex- and obesity-related differences in adipocyte size and storage capacity of each fat compartment.

The aim of this study was to investigate whether lipolysis and LPL activity were different within subcutaneous and intra-abdominal adipose tissue in men, and, if such a difference existed, whether it persisted through a wide range of abdominal adiposity values. Omental and subcutaneous adipose tissue adipocyte size, LPL activity as well as basal, isoproterenol-, forskolin-, and dibutyryl cyclic adenosine monophosphate (cAMP)–stimulated lipolysis were measured in fat samples obtained from 33 men undergoing surgery. We tested the hypothesis that lipolysis rates would be higher in the omental fat depot than in subcutaneous adipose tissue and that this difference would persist across the spectrum of abdominal adiposity values.

2. Subjects and methods

2.1. Subjects

Men of this study were recruited for studies on adipose tissue metabolism through the surgery schedule for biliopancreatic diversion at the Laval Hospital (Laval University, Quebec City, Quebec, Canada) or through the general surgery schedule at the Laval University Medical Research Center. Patients who were using hormonal treatments (androgens) or had any identified chronic diseases including diagnosed cardiovascular disease, cancer, and cachexia were excluded. Thirty-three men aged 22.6 to 61.2 years were undergoing general surgery, including cure for umbilical hernia (n = 7), endocholecystectomia (n = 2), and sigmoid restriction (n = 2), or biliopancreatic diversion for the treatment of morbid obesity (n = 22), which consists of bypassing the small intestine and diverting the bile and pancreatic juice to the distal ileum, leading to malabsorption [25,26]. One subject was treated with domperidone. Some subjects also received medication for diabetes (n = 9), hypertension (n = 15), and dyslipidemia (n = 6). Medications taken for diabetes included sulfonylurea (n = 1) or metformin (n = 9). Two patients were taking insulin and rosiglitazone. The medical ethics committees of Laval University and Laval University Medical Research Center approved this study. Written informed consent was provided by all subjects before their inclusion in the study. According to standardized procedures, body weight, height, and waist circumference measurements were obtained.

2.2. Adipose tissue sampling

Adipose tissue samples were taken during the surgery at the site of incision (subcutaneous adipose tissue) and from the greater omentum (epiploon, omental adipose tissue). Samples were immediately transported to the laboratory in 0.9% saline preheated at 37°C. The fresh biopsy specimen was used to achieve the adipocyte isolation and the residual tissue was immediately frozen at −80°C for subsequent analyses.

2.3. Adipocyte isolation, lipolysis, and LPL activity

Tissue samples were digested with collagenase type I in Krebs-Ringer-Henseleit buffer for 45 minutes at 37°C according to a modified version of the Rodbell method [27]. After being filtered through nylon mesh, the adipocyte suspensions were washed 3 times with Krebs-Ringer-Henseleit buffer. A contrast microscope attached to a camera and computer interface helped visualize mature adipocyte suspensions, thus allowing cell size measurements. Pictures were taken, and for each sample, 250 adipocyte diameters were measured by using the Scion Image software (Frederick, MD).

Lipolysis experiments were conducted by incubating isolated cell suspensions for 2 hours at 37°C with or without β-adrenergic receptor agonist isoproterenol (10^{-5} to 10^{-10} mol/L), dibutyryl cAMP (10^{-3} mol/L), or forskolin (10^{-5} mol/L). Measurements of glycerol release in the medium were made by bioluminescence using the nicotinamide adenine dinucleotide hydroxide–linked bacterial luciferase assay [28], a Berthold Microlumat plus bioluminometer (LB 96 V) and the WinGlow software (EG&G, Wildbad, Germany). The average coefficient of variation for duplicate glycerol release measurements was 13.6%. Dole extraction was used to measure lipid weight of the cell suspension in lipolysis experiments. Lipolysis results were expressed as micromoles glycerol released per 10^6 cells every 2 hours or as fold response over basal level.

Lipoprotein lipase activity was determined in 30- to 50-mg frozen adipose tissue samples by the method of Taskinen et al [29]. After incubating the sample in Krebs-Ringer phosphate buffer and heparin at 37°C for 90 minutes, the eluates obtained were then incubated with excess concentrations of unlabeled and ^{14}C-labeled triolein in a Tris-albumin buffer emulsified with ultrasound. The reaction was carried out at 37°C for 60 minutes with agitation. Afterward, the Belfrage extraction procedure was used to isolate the free fatty acids liberated from triolein by the LPL reaction. Lipoprotein lipase activity was stimulated by apolipoprotein C-II from porcine plasma, and unpasteurized cow's milk was used as an internal LPL activity standard for interassay variations. Activity results were expressed in nanomoles of oleate per 10^6 cells per hour.

2.4. Blood lipids, glucose and insulin

Fasting cholesterol and triglyceride levels were measured in plasma and lipoprotein fractions with a Technicon RA analyzer (Bayer, Etobicoke, Ontario, Canada) by means of enzymatic methods, as described before [30]. Plasma very low-density lipoproteins were isolated by ultracentrifugation, and the HDL fraction was obtained by precipitation of the LDLs from the infranatant with heparin and $MnCl_2$ [30,31]. The infranatant's cholesterol content was measured before and after precipitation, the difference of those 2 measures expressing LDL cholesterol concentration. A colorimetric assay (Sigma, St Louis MO) and radioimmunoassay (Linco Research, St Charles, MO) were used to measure fasting plasma glucose and insulin levels, respectively. The homeostasis model assessment (HOMA) insulin resistance index was calculated by using the formula: fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 [32].

2.5. Statistical analyses

Paired t tests were used to compare omental and subcutaneous adipocyte size, LPL activity, and lipolysis in the entire sample as well as in each tertile of waist circumference or in body mass index (BMI) categories. Stratification of the sample according to waist circumference tertiles was performed by using the following values: less than or equal to 124, 125 to 150, greater than or equal to 151 cm. As for BMI, the sample was stratified using the following values: less than 30, between 30 and 49, and greater than or equal to 50 kg/m^2. Age, weight, BMI, waist circumference, and blood lipid/glucose homeostasis values were compared among waist circumference or BMI categories by using 1-way analysis of variance (ANOVA) tests. Welch ANOVA was used when the Levene test ($P < .05$) revealed unequal variances. For fasting plasma insulin values, normality could not be reached and nonparametric Wilcoxon test was used for this variable. Tukey-Kramer honestly significantly different tests were used to compare the mean values of adipocyte size, LPL activity, and lipolysis among each waist circumference and BMI category. All variables that were not normally distributed according to a significant Shapiro-Wilk test ($P < .05$) were $\log_{10}$-transformed in statistical analyses when necessary. When normal distributions could not be achieved with this transformation, values were transformed with the Box-Cox formula. The analyses were conducted using the JMP statistical software (SAS Institute, Cary, NC).

3. Results

Physical characteristics as well as lipid profile and adipose tissue metabolism values of the 33 men of the study are shown in Table 1. Men were obese according to their mean BMI value (44.5 ± 13.0 kg/m^2), but the sample exhibited a normal blood lipid profile on average. Twelve men were characterized by a fasting plasma glucose value greater than or equal to 6.1 mmol/L [33].

Table 1 shows that adipocyte size was not different in the omental vs the subcutaneous fat depot. Basal lipolysis was also similar between the 2 fat depots. However, LPL activity was found to be significantly higher in omental than in subcutaneous fat tissue ($P < .005$).

The sample was then separated according to tertiles of waist circumference (Table 2). Those 3 subgroups (n = 11 each) were not different according to their age and lipid profile (not shown). However, there were significant differ-

Table 1
Characteristics of men of the study (n = 33)

	Mean ± SD	Range
Age (y)	44.0 ± 10.2	22.6-61.2
Weight (kg)	138.4 ± 48.1	70.4-265.0
BMI (kg/m^2)	44.5 ± 13.0	24.6-79.1
Waist circumference (cm)	135 ± 28	92-190
Lipid profile (mmol/L)[a]		
Cholesterol	4.83 ± 0.55	3.76-5.82
LDL cholesterol	2.87 ± 0.53	1.81-4.12
Triglycerides	2.05 ± 0.87	0.58-4.11
HDL cholesterol	1.01 ± 0.22	0.69-1.72
Cholesterol/HDL cholesterol	4.96 ± 0.97	3.19-7.06
Glucose homeostasis[b]		
Glucose (mmol/L)	6.5 ± 2.5	4.4-15.9
Insulin (μU/mL)	66.0 ± 59.6	5.4-212.2
HOMA index	22.1 ± 24.7	1.2-93.9
Omental adipocyte diameter (μm)	111 ± 12	86-144
Subcutaneous adipocyte diameter (μm)	108 ± 10	89-128
Adipose tissue metabolism		
Omental basal lipolysis (μmol/10^6 cells per 2 h)	0.82 ± 0.55	0.14-2.29
Subcutaneous basal lipolysis (μmol/10^6 cells per 2 h)	0.91 ± 0.76	0.09-3.48
Omental LPL activity (nmol/10^6 cells per hour)[c]	51.45 ± 22.80	22.39-104.47
Subcutaneous LPL activity (nmol/10^6cells per hour)[c]	38.79 ± 14.65[d]	14.57-68.76

HOMA index = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5.
[a] n = 31 for these measures.
[b] n = 32 for these measures.
[c] n = 30 for these measures.
[d] $P < .005$ vs omental LPL activity.

Table 2
Physical characteristics of men of the study (n = 33) according to waist circumference tertiles

	Waist circumference tertile (cm)			*P* (ANOVA)
	≤124	125-150	≥151	
Age (y)	45.1 ± 5.0	47.3 ± 12.7	39.5 ± 10.6	NS
Weight (kg)	87.1 ± 14.6	141.1 ± 15.5[a]	187.0 ± 37.9[a,b]	<.0001[c]
BMI (kg/m^2)	30.2 ± 4.6	44.8 ± 4.1[a]	58.4 ± 8.2[a,b]	<.0001
Waist circumference (cm)	103 ± 9	136 ± 7[a]	166 ± 14[a,b]	<.0001[c]
Glucose homeostasis[d]				
Glucose (mmol/L)	5.6 ± 0.5	6.6 ± 3.2	7.3 ± 2.6	NS
Insulin (μU/mL)	12.8 ± 5.8	76.7 ± 52.1[a]	103.8 ± 61.1[a]	<.0001[e]
HOMA index	3.3 ± 1.8	24.9 ± 23.6[a]	36.3 ± 27.2[a]	<.0001

Data are expressed as mean ± SD. HOMA index = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5. NS indicates not significant.
[a] Different from value in the lower waist circumference tertile.
[b] Different from value in the middle waist circumference tertile.
[c] Welch ANOVA used when Levene test ($P < .05$) revealed unequal variances.
[d] n = 32 for these measures.
[e] Nonparametric Wilcoxon test used.

ences in weight, waist circumference, and BMI, the group with higher waist circumferences having the highest values of all 3 variables and the lowest tertile having the lowest values, as expected. Furthermore, there was a significant difference in fasting plasma insulin and HOMA index, the upper tertile having the highest values, and the lower tertile, the lowest ($P < .0001$).

No difference was observed in omental vs subcutaneous adipocyte diameter within each waist circumference tertile (Fig. 1). On the other hand, omental adipocyte diameter was found significantly higher in the middle tertile compared with the lower tertile ($P < .05$). Regarding subcutaneous adipocytes, the diameter was found to be significantly higher in the upper tertile in comparison with subjects with the lowest waist circumferences ($P < .05$). The latter category also had significantly lower values of subcutaneous adipocyte diameter than the middle tertile ($P < .05$). Interestingly, the 2 slopes converged and seemed to reach a plateau, which was especially apparent in omental adipocytes starting at waist circumference values of 125 cm and above.

As for LPL activity, we obtained significantly higher values in omental fat tissue in the second waist circumference tertile ($P = .05$) compared with subcutaneous values, and a trend for higher activity in omental fat in the lower tertile ($P = .06$) (Fig. 2A). In each fat depot taken separately, LPL activity was similar across tertiles of waist circumference. Basal lipolysis in omental adipocytes, expressed as a function of cell number (Fig. 2B), was significantly higher in the upper waist circumference tertile compared with the lower one ($P < .05$). A trend for higher values in the upper waist circumference tertile compared with the lower one was observed for basal lipolysis in subcutaneous depots and isoproterenol-stimulated lipolysis (10^{-5} mol/L) in both compartments. We also compared lipolysis values expressed in fold over basal among waist circumference tertiles (Fig. 2C). No significant regional difference between depots and among tertiles was found.

Similar results were observed when stratifying the sample according to BMI. The first group consisted of subjects with a BMI less than 30 kg/m^2, the second was characterized by a BMI between 30 and 49 kg/m^2, and the third had a BMI greater than 50 kg/m^2. Omental adipocyte diameter was significantly higher in the intermediate group than in the leaner group ($P < .05$). Once more, a plateau could be observed in adipocyte size in the 2 obese categories, corresponding to BMI values of 30 kg/m^2 and above. Subcutaneous adipocyte diameter was higher in the upper than in the lower BMI category ($P < .05$). Omental adipocyte diameter was significantly higher than that of subcutaneous cells ($P = .01$) in the middle tertile only. Lipoprotein lipase activity was also higher in omental cells, which was significant in the median category of BMI ($P = .001$). Isoproterenol-stimulated lipolysis values (10^{-5} mol/L) were significantly higher in the upper than in the lower BMI category ($P < .05$) in both omental and subcutaneous adipocytes. There was a trend for higher basal lipolysis in subcutaneous adipocytes in the upper category in comparison with the lower BMI group.

Waist circumference as well as BMI values correlated positively and significantly with a number of lipolysis measurements, expressed as a function of cell number (Table 3). Waist circumference was significantly correlated

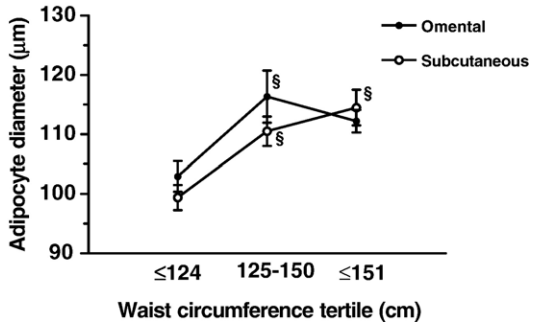

Fig. 1. Adipocyte diameter in omental vs subcutaneous adipocytes in men in the lower, middle, or upper tertile of waist circumference (n = 11 in each tertile). Error bars are SEM. [§]Different from values in the lower waist circumference tertile.

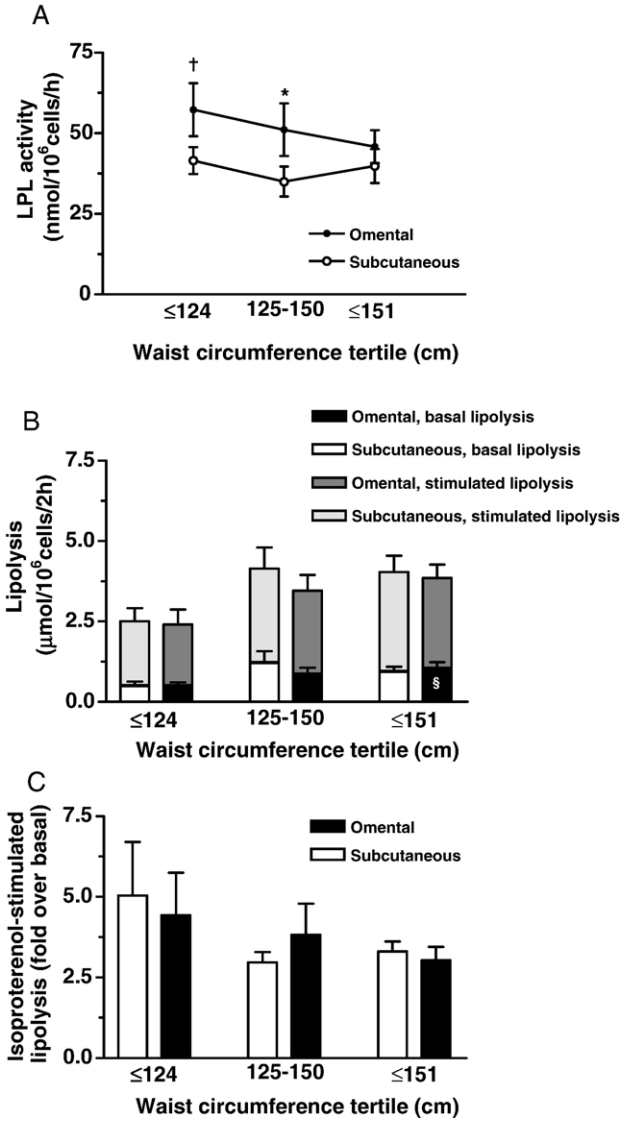

Fig. 2. Lipoprotein lipase activity (A), basal or isoproterenol-stimulated lipolysis (10^{-5} mol/L) values expressed as a function of cell number (B), and isoproterenol-stimulated lipolysis (10^{-5} mol/L), expressed in fold over basal (C) in omental vs subcutaneous adipocytes in men in the lower, middle, or upper tertile of waist circumference (n = 11 in each tertile). Error bars are SEM. *P = .05; †P = .06; §Different from values in the lower waist circumference tertile.

with isoproterenol-stimulated lipolysis (10^{-7} and 10^{-8} mol/L) in omental adipocytes (r = 0.36, P < .05 for both). Trends for positive correlations with basal and isoproterenol-stimulated lipolysis (10^{-5} mol/L) were also observed (r = 0.32, P = .07 and r = 0.31, P = .08). Basal and isoproterenol-stimulated lipolysis (10^{-5}, 10^{-6}, and 10^{-7} mol/L) in subcutaneous cells was also significantly correlated with waist circumference values (r = 0.42, P < .02; r = 0.41, P < .02; r = 0.46, P < .01; and r = 0.50, P < .005, respectively). A trend was found for a correlation with lipolysis stimulated with isoproterenol 10^{-8} and 10^{-9} mol/L (r = 0.34 and r = 0.33, respectively, P = .06 for both). As for BMI values, they were significantly correlated with values of isoproterenol-stimulated lipolysis (10^{-5}, 10^{-7}, and 10^{-8} mol/L) in omental adipocytes (r = 0.36, r = 0.39, and r = 0.38, respectively; P < .05 for all) as well as with basal and isoproterenol-stimulated lipolysis (10^{-5} to 10^{-9} mol/L) in subcutaneous fat cells (r = 0.39, P < .05; r = 0.43, P < .02; r = 0.48, P < .01; r = 0.52, P < .005; r = 0.35, P < .05; and r = 0.34, P = .05, respectively). Basal and isoproterenol-stimulated lipolysis (10^{-6} mol/L) in omental adipocytes tended to be significantly correlated with BMI values (r = 0.31, P = .08 and r = 0.32, P = .07, respectively).

The 2 obese patients taking insulin and glitazone were not extremes in the distribution of age, BMI, adipocyte size, LPL activity or basal lipolysis. Excluding these patients from the analyses had little influence on the results. Specifically, regional differences (or lack thereof) in adipocyte size and metabolism in the entire sample as well as in waist circumference tertiles were unaffected. Significant associations between waist circumference, BMI, and lipolysis measures in both depots were also unaffected.

4. Discussion

Based on the widespread idea that omental fat cells are hyperlipolytic, we tested the hypothesis that lipolysis rates would be higher in omental than in subcutaneous adipocytes in a sample of men covering a very wide range of adiposity values. However, no difference was found between the 2 depots, neither in the whole sample nor in any of the waist circumference or BMI categories. We suggest that these results could partly be explained by the similar adipocyte size found in omental and subcutaneous adipose tissue in this sample of men. Consistent with the notion that adipocyte size is a critical modulator of adipose cell metabolism [12,34], we suggest that regional differences in adipocyte size, or lack thereof, are important determinants of regional differences in adipose tissue metabolism. This study is the first to examine omental and subcutaneous adipose tissue/adipose cell metabolism in detail in a sample of men covering such a wide range of adiposity values (from normal weight to extremely obese).

One of our main findings is that adipocyte diameter was not different in omental vs subcutaneous adipose tissues, either in the entire sample of men or across waist circumference or BMI categories. This finding is clearly at variance with our previous observations in women [16]. Indeed, in a previous study including 55 women, omental adipocytes were clearly smaller than subcutaneous adipocytes, although the sample did not include morbidly obese women (BMI ranging from 17.2 to 41.3 kg/m^2). Although the 2 slopes of adipocyte size as a function of total body fat mass seemed to converge slightly as omental adipocyte size increased with obesity [16], only a few of those women had omental adipocytes as large as their subcutaneous fat cells. Other studies including women also found significantly higher adipocyte size in subcutaneous compared with omental fat cells [12,14,21-23]. Our finding of similar

Table 3
Correlations between waist circumference and lipolysis values, expressed as a function of cell number

	Waist circumference (cm)	BMI (kg/m^2)
Omental lipolysis (μmol/10^{6}cells per 2 h)		
Basal	0.32[a]	0.31[a]
Isoproterenol (mol/L)		
10^{-5}	0.31[a]	0.36[b]
10^{-6}	0.27	0.32[a]
10^{-7}	0.36[b]	0.39[b]
10^{-8}	0.36[b]	0.38[b]
10^{-9}	0.25	0.28
10^{-10}	0.24	0.27
Dibutyryl cAMP (10^{-3} mol/L)	0.08	0.12
Forskolin (10^{-5} mol/L)	0.12	0.18
Subcutaneous lipolysis (μmol/10^{6}cells per 2 h)		
Basal	0.42[c]	0.39[b]
Isoproterenol (mol/L)		
10^{-5}	0.41[c]	0.43[c]
10^{-6}	0.46[d]	0.48[d]
10^{-7}	0.50[e]	0.52[e]
10^{-8}	0.34[a]	0.35[b]
10^{-9}	0.33[a]	0.34[b]
10^{-10}[f]	0.25	0.26
Dibutyryl cAMP (10^{-3} mol/L)[f]	−0.11	−0.10
Forskolin (10^{-5} mol/L)[f]	0.11	0.13

Data are Pearson correlation coefficients.
[a] $P \leq .08$.
[b] $P \leq .05$.
[c] $P < .02$.
[d] $P < .01$.
[e] $P < .005$.
[f] n = 32 for these values.

adipocyte size in omental and subcutaneous fat depots in men, even in the normal-weight to moderately obese group, may reflect the well-documented sex difference in visceral adipose tissue accumulation [35]. In fact, a close survey of the literature indicates that numerous studies in men found no difference in adipocyte size between the omental and subcutaneous depots [12,14,18,21-23]. In another study, no difference was observed between omental and subcutaneous adipocyte size in obese subjects, but significantly larger subcutaneous fat cells were observed in nonobese subjects. In most studies, it is interesting to notice that although not of statistical significance, the subcutaneous adipocytes were slightly larger than omental fat cells in samples with a mean BMI less than 40 kg/m^2 [18,22] and that the omental fat cells tended to be larger in samples with a mean BMI above 44 kg/m^2 [12,14,19,21,23]. This could suggest that as opposed to women, who display larger subcutaneous adipocytes throughout the adiposity spectrum, the point where omental adipocytes become as large as subcutaneous adipocytes in men seems to occur at much lower adiposity values.

Previous studies investigated whether regional differences in lipolysis were found both in obese and in nonobese subjects. One of these studies reported that catecholamine-induced lipolysis (expressed in percent response) was higher in omental than in subcutaneous fat cells, but only in obese subjects [19]. Higher lipolysis responsiveness was explained by a higher β_3-adrenoceptor activity in omental cells. Indeed, the authors suggested that as the intra-abdominal fat compartment increased in size, β_3-adrenoceptor function became more pronounced, resulting in an increase in lipolytic activity. The obese group of the latter study corresponded to subjects from the middle waist circumference tertile of the present sample [19]. In Fig. 2C, we can observe a trend for a similar regional difference, which would only be attributable to $\beta_{1\text{-}2}$-adrenoceptor activity (stimulated by isoproterenol) because we have not tested the β_3-adrenoceptor sensitivity in our experiments. The absence of regional difference in the lower waist circumference tertile is consistent with the lack of difference in the nonobese group [19]. Moreover, positive and significant correlations were found between adiposity values and several lipolysis measures, expressed as a function of cell number. These results, and that subcutaneous and omental adipocyte size were higher in the upper and middle waist circumference or BMI categories compared with the lower adiposity groups, suggest that with increasing adiposity, fat cells enlarge and thus may release more fatty acids, again supporting the notion that adipocyte size strongly influences fat cell metabolism [34].

Lipoprotein lipase activity was found to be significantly higher in omental adipocytes in the median categories of waist circumference and BMI. A trend for higher values in omental fat cells was found in the lower tertile of waist circumference. This is consistent with previous studies reporting higher LPL activity in omental cells. Interestingly, the studies reporting such a difference are those that included a majority of male subjects [18,24]. This result could reflect a higher capacity to store fat in the omental depot in lean to moderately obese men compared with previous studies suggesting higher fat storage capacities in subcutaneous compartments in women [16,23]. Those results are also consistent with the fact that men are typically characterized by fat accumulation in the intra-abdominal region (android type of obesity) compared with women who store more of their fat in the femoral subcutaneous region (gynoid type of obesity). For similar adiposity, men have twice the amount of visceral adipose tissue area than women [35] and are more affected by metabolic complications associated with this pattern of fat distribution. However, the absence of regional difference in LPL activity in the upper waist circumference tertile suggests that as waist circumference increases, storage capacity becomes limited in omental fat cells, which is consistent with the plateau observed in omental adipocyte size. This plateau is in agreement with previous studies suggesting that when fat cells have reached a critical weight, they increase in number, but not in size [36]. This plateau could reflect a limitation in the fat storage capacity of those adipocytes, thus implying that excess fat could be stored elsewhere. Finally, the finding that LPL activity is higher in omental adipocytes and that there is no regional difference in lipolysis rates could reflect a net physiologic balance toward

fat storage in the omentum rather than triglyceride mobilization through lipolysis. This indirectly suggests increased rates of visceral adipose tissue accumulation in the subjects of the lower and middle waist circumference tertiles.

Some limitations in this study should be acknowledged. First of all, waist circumference could not distinguish visceral fat from subcutaneous adipose tissue accumulation. Visceral and subcutaneous adipose tissue areas were not measured by radiologic imaging, which would have been more precise and relevant. However, computed tomography would not have generated valid results in men of the study that were in the morbidly obese range. Moreover, the relatively small number of normal-weight subjects in the study could also have underestimated the correlations between obesity measures and adipose cell metabolism. Obtaining omental fat samples from lean men is a difficult task, and further studies are warranted to clearly elucidate regional differences in adipocyte metabolism in this population. Finally, inconsistencies between this and other studies on abdominal adipose tissue metabolism and regional differences may also be explained by differences in the anatomic location chosen for fat sampling.

In summary, in our sample of 33 men covering a very wide range of adiposity, regional differences in lipolysis rates were found neither in the whole sample nor in any of the waist circumference or BMI categories.

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